



⑪ Publication number:

**0 252 713
B1**

⑫

EUROPEAN PATENT SPECIFICATION④⑤ Date of publication of the patent specification:
12.09.90⑤① Int. Cl.⁶: **C07D 209/34**, C07D 209/96,
A61K 31/405

②① Application number: 87305984.4

②② Date of filing: 07.07.87

⑤④ Indolllnone derivatives.

③⑩ Priority: 10.07.86 PCT/US86/01429

⑦③ Proprietor: **PFIZER INC.**, 235 East 42nd Street, New
York, N.Y. 10017(US)④③ Date of publication of application:
13.01.88 Bulletin 88/2⑦② Inventor: **Howard, Harry Ralph, Jr.**, 272 West Woods
Terrace, Bristol Connecticut(US)
Inventor: **Sarges, Reinhard**, River Road, Mystic
Connecticut(US)④⑤ Publication of the grant of the patent:
12.09.90 Bulletin 90/37④④ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE⑦④ Representative: **Wood, David John et al**, **PFIZER
LIMITED**, Ramsgate Road, Sandwich, Kent
CT13 9NJ(GB)⑤⑥ References cited:
EP-B- 0 022 317
DE-A- 2 727 046
US-A- 3 393 208
US-A- 3 821 383

CHEMICAL ABSTRACTS, vol. 103, no.11,
September 16,1985, Columbus, OH (US); BOLOTOV,
V.V. et al. "Synthesis, properties and biological activity
of 3,3,3',3'-tetraphenyl-5,5'-bis(2-oxoindoline-1-acetic
acids)" page 596, column 2, abstract-no. 87 739q
-methoxy-m-diamines and p-methoxy- and
p-chlorophenols" trength fibre, e.g. glass fibre"
CHEM. 1977, 000
CHEMICAL ABSTRACTS, vol. 97, no. 21, November 22,
Columbus, Ohio, USA TAKEDA CHEMICALS
INDUSTRIES, LTD. "Spiroindolllnone derivatives"
page 808, column 2, abstract-no. 182 208g

EP 0 252 713 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

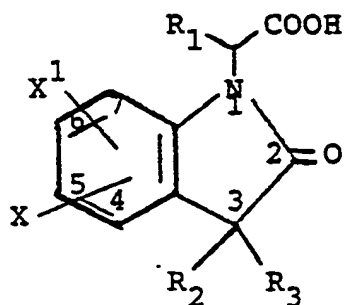
EP 0 252 713 B1

Description

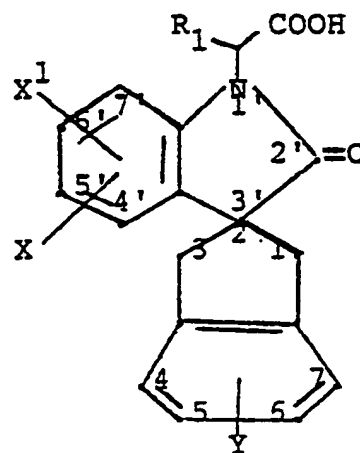
This invention relates to new indolinone derivatives of interest to those in the field of medicinal chemistry and chemotherapy. More particularly, it is concerned with a novel series of oxindole-1-alkanoic acid compounds for the control of certain chronic complications arising from diabetes mellitus (e.g., diabetic cataracts, retinopathy and neuropathy).

Past attempts to obtain new and better oral antidiabetic agents have, for the most part, involved an endeavor to synthesize new compounds that lower blood sugar levels. More recently, several studies have been conducted concerning the effect of various organic compounds in preventing or arresting certain chronic complications of diabetes, such as diabetic cataracts, neuropathy and retinopathy, etc. For instance, K. Sestanji et al. in U.S. Patent No. 3,821,383 discloses that certain aldose reductase inhibitors like 1,3-dioxo-1H-benz[d,e]isoquinoline-2(3H)-acetic acid and some closely-related derivatives thereof are useful for these purposes even though they are not known to be hypoglycemic. These compounds function by inhibiting the activity of the enzyme aldose reductase, which is primarily responsible for catalyzing the reduction of aldoses (like glucose and galactose) to the corresponding polyols (such as sorbitol and galactitol) in the human body. In this way, unwanted accumulations of galactitol in the lens of galactosemic subjects and of sorbitol in the lens, retina, peripheral nervous system and kidney of diabetic subjects are prevented or reduced. As a result, these compounds control certain chronic diabetic complications, including those of an ocular nature, since it is already known in the art that the presence of polyols in the lens of the eye leads to cataract formation and concomitant loss of lens clarity.

The present invention relates to novel oxindole-1-alkanoic acid compounds useful as aldose reductase inhibitors for the control of certain chronic complications arising in a diabetic subject. More specifically, the novel compounds of this invention are selected from the group consisting of 3-substituted 2-oxo-indoline-1-alkanoic acids of the formulae:



and



I

II

and the C₁-C₈ alkyl esters and primary amide derivatives thereof, and the base salts of said acids with pharmacologically acceptable cations, wherein X is hydrogen and X' is hydrogen, hydroxy, fluorine, chlorine, bromine, C₁-C₄ alkyl or C₁-C₄ alkoxy; or X and X', when taken separately, are each chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy, and when taken together are -OCH₂(CH₂)_nO- at the 4,5-, 5,6- or 6,7-positions of the molecule wherein n is zero or one; R₁ is hydrogen or methyl; R₂ is hydrogen, C₁-C₄ alkyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two chlorine substituents on the phenyl ring; R₃ is naphthylmethyl, furyl, thenyl, benzothienylmethyl, benzoxazolylmethyl, benzothiazolylmethyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two identical or non-identical substituents on the phenyl ring, said identical substituents being fluorine, chlorine, bromine, trifluoromethyl, C₁-C₄ alkyl or C₁-C₄ alkoxy and said non-identical substituents being chlorine, methyl, methoxy or trifluoromethyl; and Y is hydrogen, fluorine, chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy. These novel compounds are aldose reductase inhibitors and therefore, possess the ability to reduce or inhibit sorbitol formation in the lens and peripheral nerves of diabetic subjects.

One group of compounds of the present invention of interest is that of formula I wherein X is hydrogen; X' is hydrogen, hydroxy, fluorine, chlorine or C₁-C₄ alkoxy; X and X', when taken separately, are each C₁-C₄ alkoxy; R₁ is hydrogen or methyl; R₂ is hydrogen, C₁-C₄ alkyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is ring-substituted with up to two chlorine

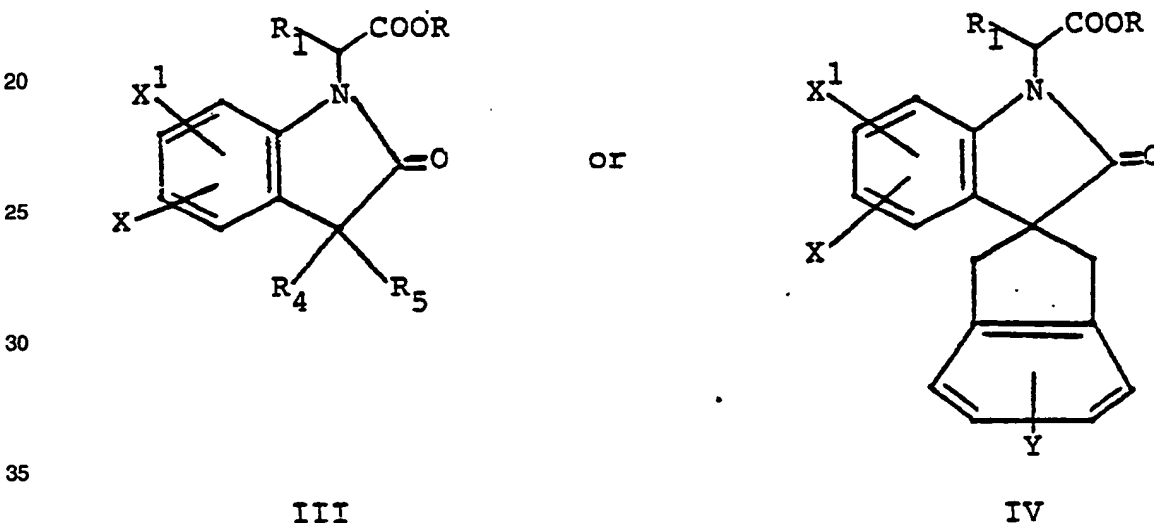
EP 0 252 713 B1

substituents on the phenyl ring; and R₃ is phenylalkyl as just hereinbefore defined for R₂. Preferred compounds within this group include those where X is hydrogen, X' is hydrogen, hydroxy, chlorine or methoxy, R₁ and R₂ are each hydrogen and R₃ is 3,4-dichlorobenzyl or 3,4-dichloro- α -methylbenzyl.

Another group of compounds of the present invention of interest is that of formula II wherein X is hydrogen; X¹ is hydrogen, hydroxy, chlorine or methoxy; R₁ is hydrogen and Y is hydrogen, hydroxy, chlorine or methoxy. Preferred compounds within this group include those where X, X¹ and R₁ are each hydrogen and Y is hydrogen or chlorine at the 5(6)-position of the molecule.

Of special interest are such typical and preferred member compounds of the invention as 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, 5-chloro-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, 3-(3,4-dichlorobenzyl)-6-methoxy-2-oxo-indoline-1-acetic acid, 3-(3,4-dichlorobenzyl)-6-hydroxy-2-oxo-indoline-1-acetic acid and 3-(3,4-dichloro- α -methylbenzyl)-2-oxo-indoline-1-acetic acid. These particular compounds are highly potent aldose reductase inhibitors.

In accordance with the process employed for preparing the novel compounds of this invention, an appropriately substituted 2-oxo-indoline-1-alkanoic acid aralkyl ester of the formula:



wherein X, X¹, Y and R₁ are all as previously defined, R is an aralkyl group such as benzyl or a similar blocking group such as *m*-xylyl or *p*-chlorobenzhydryl and the like, R₄ and R₅ are each as previously defined for R₂ and R₃ except that R₄ is always other than hydrogen, or R₄ and R₅, when taken together, form the divalent groups =R₆ where R₆ is naphthylidene, furfurylidene, thenylidene, benzothienylmethylidene, benzoxazolymethylidene, benzothiazolymethylidene or phenylalkylidene having up to three carbon atoms in the alkylidene moiety wherein said phenylalkylidene is optionally substituted with up to two identical or non-identical substituents on the phenyl ring, said identical substituents being fluorine, chlorine, bromine, trifluoromethyl, C₁-C₄ alkyl or C₁-C₄ alkoxy and said non-identical substituents being chlorine, methyl, methoxy or trifluoromethyl, is subjected to the action of hydrogen in the presence of a noble metal catalyst until the reduction to form the desired final product is substantially complete. This hydrogenolysis reaction is normally conducted in a reaction-inert organic solvent at a pressure ranging from 103.4 to 344.7 kPa (15 to 50 psi) hydrogen and at a temperature that is in the range of from about 0°C. up to about 50°C. and preferably from about 15°C. to about 35°C. Preferred reaction-inert organic solvents for use in this connection include lower alkanols such as methanol, ethanol and isopropanol, lower dialkyl ethers such as diethyl ether, diisopropyl ether and di-n-butyl ether, as well as lower alkyl esters of lower alkanolic acids such as methyl acetate, ethyl acetate, isopropyl acetate, methyl propionate and ethyl propionate. The organic solvent will preferably contain a minor amount (e.g. 10-30% by weight) of an acid, which is usually an organic acid like glacial acetic acid or a similar lower alkanolic acid, but it can also be a substantially anhydrous mineral acid like phosphoric acid or sulfuric acid. Noble metal catalysts as employed herein include platinum, palladium, rhodium, rhodium and ruthenium, either of the supported or non-supported type, as well as the known catalytic compounds thereof, such as the oxides and chlorides. The catalyst may be preformed or else formed *in situ* by the pre-reduction of an appropriate salt or oxide of the catalytic compound. Preferred catalysts for use in the reaction include platinum oxide and even more especially, palladium-on-carbon. Upon completion of the hydrogenolysis step, the desired oxindole-1-alkanolic acid final product is readily recovered from the resulting reaction mixture, viz., by first removing the catalyst from the reaction mixture by means of filtration and then concentrat-

EP 0 252 713 B1

ing the resulting filtrate to an oil or foam by means of evaporation under reduced pressure, followed by recrystallization from a suitable solvent system.

Compounds of the invention wherein X^1 of structural formulae I and II is hydroxy can be readily prepared from the corresponding compounds where X^1 is methoxy by simply dealkylating same in accordance with standard techniques well known to those skilled in the art. For instance, the use of boron tribromide in this connection readily converts 3-(3,4-dichlorobenzyl)-6-methoxy-2-oxo-indoline-1-acetic acid to the corresponding 6-hydroxy compound. Moreover, certain compounds of the invention (of structural formulae I-II) having a ring substituent (X^1) which is lower alkoxy of more than one carbon atom can alternatively be prepared from the corresponding methoxy compounds by first converting same to the corresponding hydroxy derivatives and then alkylating the latter with, for example, ethyl iodide or isopropyl bromide in a manner well known to those skilled in the art. As previously indicated, the oxindole-1-alkanoic acid final products (of structural formulae I-II) can be used as such for the therapeutic purposes of this invention or else simply converted to the corresponding lower alkyl ester and primary amide derivatives thereof in accordance with conventional techniques.

The lower alkyl esters of the 3-substituted 2-oxo-indole-1-alkanoic acids of this invention are generally prepared by condensation of the acid with the appropriate alcohol in the presence of an acid catalyst in accordance with conventional organic procedure. The primary amide derivatives are readily prepared, for example, by treating the corresponding acid chloride with ammonia under basic conditions and thereafter isolating the amide final product.

The aralkyl ester starting materials (of structural formulae III-IV) required for preparing the 3-substituted 2-oxo-indoline-1-alkanoic acid compounds of this invention, are all new compounds, which are prepared by treating the corresponding 3-substituted 2-indolinone (having a free hydrogen atom at the 1-position) with an appropriate α -haloalkanoic acid aralkyl ester of choice having the formula $ZCH(R_1)COOR$, where R and R_1 are each as previously defined in the structural formulae for the aralkyl esters and Z is either chlorine, bromine or iodine. This particular reaction is normally carried out in the presence of a basic condensing agent such as an alkali metal hydride, alkanolate or amide, or an alkali metal-alkyl or aryl compound, as the case may be, and is usually conducted in a reaction-inert polar organic solvent, preferably using one of the N,N-di-(lower alkyl)lower alkanamides. Preferred solvents in this connection include N,N-dimethylformamide, N,N-diethylformamide, N,N-di(n-propyl)formamide, N,N-dimethylacetamide, N,N-diethylacetamide and N,N-dimethylpropionamide. In general, substantially equimolar amounts of reactant and reagent are employed (i.e., from about 0.80 to about 1.25 mole of halo-reagent with respect to the 3-substituted 2-indolinone starting material) and the reaction is effected at a temperature that is in the range of from about 5°C. up to about 35°C. for a period of about 15 minutes up to about two hours. The reaction is usually conducted at room temperature for a period of time that is ordinarily less than about one hour. The basic condensing agents required for the reaction are all selected from the class of alkali metal bases previously enumerated which are sufficiently strong to form salts with the weakly acidic 3-substituted 2-indolinones and yet mild enough not to degrade the organic molecule under the conditions of the reaction. Such basic condensing agents include, for example, sodium hydride, lithium hydride and potassium hydride, as well as sodium and potassium lower alkanolates like sodium methylate and potassium *tert*-butoxide, as well as alkali metal amides like sodamide, lithium amide and potassium amide. Upon completion of the reaction, the desired 3-substituted 2-oxo-indoline-1-alkanoic acid aralkyl esters are readily recovered from the reaction mixture by the use of standard techniques well-known to those skilled in the art, e.g., the reaction mixture may be first diluted with water and then extracted with a suitable solvent such as methylene chloride or chloroform, etc., to ultimately afford the desired intermediate esters after first removing the solvent from the organic extract.

The 3-substituted 2-indolinone compounds that are employed as starting materials in the above described reaction are all new compounds which are prepared by a number of different methods. For instance, 3-substituted 2-indolinone compounds where the 3-substituent is the divalent group $=R_6$ are prepared by condensing the corresponding 2-indolinone compounds with the appropriately-substituted aromatic or heteroaromatic aldehyde or ketone, such as 3,4-dichlorobenzaldehyde or 3,4-dichloroacetophenone, in a base-catalyzed manner to form the desired condensation product in accordance with the conventional methods of organic synthesis. This particular reaction is hereinafter described in some detail in the experimental section of the specification (see Preparations A-F). On the other hand, 3-substituted 2-indolinones where the 3-substituent is the disubstituted grouping R_4 and R_5 , as previously defined for structural formula III and particularly where said disubstitution is symmetrical at the 3,3-positions of the molecule, are all preferably prepared by first acetylating the 1-position of the starting 2-indolinone compound and then effecting the desired alkylation at the 3,3-positions by means of reaction with an appropriately-substituted aralkyl halide, such as 3,4-dichlorobenzyl chloride, followed by deacetylation to afford the desired 3,3-disubstituted-2-indolinone intermediate (see Preparations O, U and X). 3-Substituted 2-indolinones of structural formula IV are also prepared in a similar manner by simply substituting an appropriate α,α' -dihalo-p-xylene for the aralkyl-halide in this sequence of reactions. (see Preparations O, Q, R, S, V and W). Lastly, 3-substituted 2-indolinones of structural formula III where the 3-substituent is the disubstituted grouping R_4 and R_5 and the disubstitution at the 3,3-positions of the molecule is unsymmetrical, are best prepared by first condensing the starting 2-indolinone compound with the appropriate aromatic or heteroaromatic aldehyde or ketone fol-

EP 0 252 713 B1

lowed by subsequent catalytic reduction to the corresponding 3-monosubstituted-2-indolinone and then acetylation at the 1-position, alkylation at the 3-position (with an appropriate alkyl halide such as methyl iodide) and deacetylation at the 1-position to ultimately afford the desired 3,3-disubstituted-2-indolinone intermediate (see Preparations, N, P, T and Y).

5 The 2,3-dihydro-2-oxo-indoles (i.e., 2-indolinones) required as the ultimate starting materials for preparing all the compounds of this invention via the previously described reaction schemes are, for the most part, known compounds and are either readily available commercially like 2,3-dihydro-2-oxo-indole (oxindole) and 5-chloro-oxindole, or else they can easily be synthesized by those skilled in the art from common organic chemicals by using conventional methods of organic synthesis (e.g., see literature references to 6-fluoro-oxindole, 5,6-dimethoxyoxindole and 6-methoxyoxindole in Preparations C-E).

10 The chemical bases which are used as reagents in this invention to prepare the aforementioned pharmaceutically acceptable base salts are those which form non-toxic base salts with the herein described 3-substituted 2-oxo-indoline-1-alkanoic acid compounds such as 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, for example. These particular non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by simply treating the aforementioned 3-substituted 2-oxo-indoline-1-alkanoic acid compounds with an aqueous solution of the desired pharmacologically acceptable cation, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

As previously indicated, the 3-substituted 2-oxo-indoline-1-alkanoic acid compounds of this invention are readily adapted to therapeutic use as aldose reductase inhibitors for the control of chronic diabetic complications, in view of their ability to reduce lens sorbitol levels in diabetic subjects to a statistically significant degree. For instance, 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, a typical and preferred agent of the present invention, has been found to inhibit the formation of sorbitol levels in diabetic rats to a significantly high degree when given by the oral route of administration at dose levels ranging from 0.75 mg./kg. to 20 mg./kg. Furthermore, the herein described compounds of this invention can be administered by either the oral or parenteral routes of administration. In general, these compounds are ordinarily administered in dosages ranging from about 0.15 mg. to about 15 mg. per kg. of body weight per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen.

These compounds may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and such administration can be carried out in either single or multiple dosages. More particularly, the compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents- or fillers, sterile aqueous media and various non-toxic organic solvents. In general, the compounds of the invention will be present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition to provide the desired unit dosage.

For oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include the high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes, and if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, solutions of these 3-substituted 2-oxo-indoline-1-alkanoic acids in sesame or peanut oil or in aqueous propylene glycol or N,N-dimethylformamide may be employed, as well as sterile aqueous solutions of the corresponding water-soluble, alkali metal or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art. Additionally, it is also possible to administer the aforesaid oxindole-1-alkanoic acid compounds topically via an appropriate ophthalmic solution applied dropwise to the eye.

The activity of the compounds of the present invention, as agents for the control of chronic diabetic complications, is determined by their ability to successfully pass one or more of the following standard biological or pharmacological tests, viz., (1) measuring their ability to inhibit the enzyme activity of isolated

EP 0 252 713 B1

- aldose reductase; (2) measuring their ability to reduce or inhibit sorbitol accumulation in the sciatic nerve of acutely streptozotocinized (i.e., diabetic) rats; (3) measuring their ability to reverse already-elevated sorbitol levels in the sciatic nerve and lens of chronic streptozotocin-induced diabetic rats; (4) measuring their ability to prevent or inhibit galactitol formation in the lens of acutely galactosemic rats, and (5) measuring their ability to delay cataract formation and reduce the severity of lens opacities in chronic galactosemic rats.

PREPARATION A

- To a well-stirred suspension consisting of 12.5 g. (0.091 mole) of 2,3-dihydro-2-oxo-indole(oxindole) and 16.0 g. (0.091 mole) of 3,4-dichlorobenzaldehyde in 30 ml. of methanol, there were carefully added 7.6 ml. of pyrrolidine in a dropwise manner (the reaction is exothermic). The resulting reaction mixture was then heated on a steam bath for a period of 15 minutes, followed by cooling to room temperature (-20°C.). The precipitated orange product was recovered by means of filtration, washed with 30 ml. of cold methanol and dried in vacuo to constant weight to ultimately afford 21.4 g. (81%) of pure 3-(3,4-dichlorobenzylidene)-2-indolinone, m.p. 183-186°C.; mass spectrum, m/e 291/289.
- Anal. Calcd. for $C_{15}H_{19}NOCl_2$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.16; H, 3.28; N, 4.85.

PREPARATION B

- The procedure described in Preparation A was repeated except that 5-chloro-oxindole was the starting material employed in place of oxindole, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 5-chloro-3-(3,4-dichlorobenzylidene)-2-indolinone, m.p. 272-275°C. after recrystallization from methanol. The yield of pure product was 82% of the theoretical value.

PREPARATION C

- The procedure described in Preparation A was repeated except that 6-fluoro-oxindole [M. Protiva et al., Collect. Czech. Chem. Commun., Vol. 44, p. 2108 (1979)] was the starting material employed in place of oxindole, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-6-fluoro-2-indolinone, isolated as the quarter-hydrate, m.p. 217-220°C. after recrystallization from methanol. The yield of pure product was 84% of the theoretical value.

PREPARATION D

- The procedure described in Preparation A was repeated except that 5,6-dimethoxyoxindole [G. Walker, J. Am. Chem. Soc., Vol. 77, p. 3844 (1955)] was the starting material employed in place of oxindole, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-5,6-dimethoxy-2-indolinone, m.p. 248-250°C. (decomp.) after recrystallization from methanol. The yield of pure product was 88% of the theoretical value.

PREPARATION E

- The procedure described in Preparation A was repeated except that 6-methoxyoxindole [A. Beckett et al., Tetrahedron, Vol. 24, p. 6093 (1968)] was the starting material employed in place of oxindole using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-6-methoxy-2-indolinone, m.p. 189-191°C. after recrystallization from methanol. The yield of pure product was 85% of the theoretical value.

PREPARATION F

- The procedure described in Preparation A was repeated except that 3,4-dichloro-acetophenone was the starting material employed in place of 3,4-dichlorobenzaldehyde, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichloro- α -methylbenzylidene)-2-indolinone, m.p. 233-235°C. after recrystallization from methanol. The yield of pure product was 82% of the theoretical value.

PREPARATION G

- A stirred mixture consisting of 480 mg. (0.01 mole) of pentane-washed sodium hydride dispersed in mineral oil (50% oil dispersion) and 40 ml. of dry N,N-dimethylformamide was treated with 2.9 g. (0.097 mole) of 3-(3,4-dichlorobenzylidene)-2-indolinone (the product of Preparation A) under a dry nitrogen atmosphere to give a brown homogeneous solution within a period of 20 minutes. To the stirred brown solution,

EP 0 252 713 B1

there were then added 2.29 g. (0.01 mole) of benzyl bromoacetate at room temperature and the resulting reaction mixture was thereafter stirred at 25°C. for a period of 48 hours. Upon completion of this step, the final organic solution thus obtained was diluted with water (~100 ml.) and then extracted with five-100 ml. portions of chloroform. The combined organic extracts were thereafter washed with water and saturated aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a yellow solid (yield, 4.75 g.) as the residue. The latter material was subsequently recrystallized from chloroform to afford 2.28 g. (52%) of pure cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester, isolated as the semihydrate, m.p. 190-192°C.; mass spectrum, m/e 439/437.

Anal. Calcd. for $C_{24}H_{17}NO_3Cl_2 \cdot 0.5H_2O$: C, 64.44; H, 4.06; N, 3.66. Found: C, 64.17; H, 4.29; N, 3.13.

PREPARATION H

The procedure described in Preparation G was repeated except that 5-chloro-3-(3,4-dichlorobenzylidene)-2-indolinone (the product of Preparation B) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar portions as before. In this particular case, the corresponding final product obtained was 5-chloro-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester, isolated as the quarter-hydrate, m.p. 196-198°C. after recrystallization from ethyl acetate. The yield of pure product was 82% of the theoretical value.

PREPARATION I

The procedure described in Preparation G was repeated except that 3-(3,4-dichlorobenzylidene)-6-fluoro-2-indolinone (the product of Preparation C) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-6-fluoro-2-oxo-indoline-1-acetic acid, benzyl ester, isolated as the semihydrate, m.p. 198-200°C. after recrystallization from N,N-dimethylformamide/water. The yield of pure product was 78% of the theoretical value.

PREPARATION J

The procedure described in Preparation G was repeated except that 3-(3,4-dichlorobenzylidene)-5,6-dimethoxy-2-indolinone (the product of Preparation D) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-5,6-dimethoxy-2-oxo-indoline-1-acetic acid benzyl ester, m.p. 213-215°C. after recrystallization from N,N-dimethylformamide/water. The yield of pure product was 93% of the theoretical value.

PREPARATION K

The procedure described in Preparation G was repeated except that 3-(3,4-dichlorobenzylidene)-6-methoxy-2-indolinone (the product of Preparation E) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-6-methoxy-2-oxo-indoline-1-acetic acid benzyl ester, m.p. 146-148°C. (decomp.) after recrystallization from N,N-dimethylformamide/water. The yield of pure product was 83% of the theoretical value.

PREPARATION L

The procedure described in Preparation G was repeated except that benzyl 2-chloropropionate was the reagent employed in place of benzyl bromoacetate, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-(α -methyl)acetic acid benzyl ester (in the form of a gum). The yield of pure product was 13% of the theoretical value.

PREPARATION M

The procedure described in Preparation G was repeated except that 3-(3,4-dichloro- α -methylbenzylidene)-2-indolinone (the product of Preparation F) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichloro- α -methylbenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester, m.p. 120-122°C. after recrystallization from methylene chloride. The yield of pure product was 18% of the theoretical value.

EP 0 252 713 B1

PREPARATION N

A suspension consisting of 5.0 g. (0.0164 mole) of 3-(3,4-dichloro- α -methylbenzylidene)-2-indolinone (the product of Preparation M) and 1.0 g. of 5% palladium-on-carbon catalyst in 100 ml. of ethanol and 100 ml. of ethyl acetate was hydrogenated on a Parr shaker at 50 p.s.i. pressure for a period of four hours (20 p.s.i. hydrogen uptake was observed). The reaction mixture was then filtered through Celite (diatomaceous earth) to remove the catalyst, and the resulting filtrate subsequently concentrated in vacuo to give a red-orange gum that slowly crystallized on standing for a period of approximately 16 hours (overnight). In this way, there were readily obtained 5.2 g. of 3-(3,4-dichloro- α -methylbenzyl)-2-indolinone, m.p. 127-129°C. The product was further characterized by means of mass spectroscopy, nuclear magnetic resonance data and thin layer chromatography.

PREPARATION O

N-Acetyl-2-indolinone was prepared according to the procedure described by G. Walker in the Journal of the American Chemical Society, Vol. 77, p. 3844 (1955). This involved refluxing a mixture of 50 g. (0.376 mole) of oxindole in 500 ml. of acetic anhydride for five hours, then cooling and filtering the resulting crystalline product. In this way, there were eventually obtained 64.5 g. (98%) of pure N-acetyl-2-indolinone, m.p. 124-126°C. (literature m.p. 127°C., according to the aforesaid reference).

PREPARATION P

The procedure described in Preparation O was repeated except that 3-(3,4-dichloro- α -methylbenzyl)-2-indolinone (the product of Preparation N) was the starting material employed in place of oxindole, using the same weight-volume proportions of reactant and reagent as before. This involved refluxing a mixture of 5.2 g. (0.0164 mole) of the indolinone in 100 ml. (1.06 mole) of acetic anhydride for a period of five hours, followed by cooling to room temperature (-20°C.) and subsequent evaporation of the solution under reduced pressure to afford a dark red-brown oil. The latter material was then dissolved in 150 ml. of ethyl acetate, washed once with water, once with saturated aqueous sodium bicarbonate solution and once with brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained 5.5 g. (97%) of pure N-acetyl-3-(3,4-dichloro- α -methylbenzyl)-2-indolinone in the form of an orange-red oil as the residue. The pure product was characterized by means of mass spectroscopy and nuclear magnetic resonance data.

PREPARATION Q

A mixture consisting of 5.0 g. (0.0306 mole) of N-acetyl-2-indolinone (the product of Preparation O) and 9.8 g. (0.0708 mole) of potassium carbonate in 100 ml. of N,N-dimethylformamide was stirred under a dry nitrogen atmosphere at 25°C., while 8.4 g. (0.0306 mole) of α,α' -dibromo-*p*-xylene (96% pure; available from the Aldrich Chemical Company, Inc. of Milwaukee, Wisconsin) was slowly added thereto. After allowing the reaction mixture to stand for four days at 25°C., the resulting mixture containing the orange solid product was poured over 300 ml. of ice water and stirred for 30 minutes, followed by suction filtration. In this way, there were eventually obtained 7.4 g. (87%) of pure 1'-acetyl-1,2-dihydro-spiro-inden[2,3']-indolin-2'-one semihydrate, m.p. 159°C. (decomp.) after first washing with water and air drying to constant weight.

Recrystallization of the latter material from aqueous N,N-dimethylformamide did not change the value of the melting point. The mass spectrum was m/e 277.

Anal. Calcd. for $C_{18}H_{15}NO_2 \cdot 0.5H_2O$: C, 75.50; H, 5.63; N, 4.89. Found: C, 75.77; H, 5.54; N, 4.92.

PREPARATION R

To 25 g. (0.178 mole) of 4-chloro-*p*-xylene heated to 130°C. and illuminated with a 100 Watt incandescent lamp, there were added with stirring 19.6 ml. (0.382 mole) of bromine in a dropwise manner over a period of 35 minutes. Upon completion of this step, the resulting reaction mixture was stirred at 130°C. for an additional 1.5 hours and then cooled to 25°C. and allowed to stir overnight (-16 hours). At this point, the excess hydrogen bromide and bromine were removed in vacuo and the residual product was fractionally distilled as a pale yellow oil to afford 23.1 g. (44%) of pure 1,2-bis(bromomethyl)-4-chlorobenzene, b.p. 128-137°C./0.6 mm. Hg; mass spectrum, m/e 296, 298, 300.

PREPARATION S

The procedure described in Preparation Q was repeated except that 1,2-bis(bromomethyl)-4-chlorobenzene (the product of Preparation R) was the alkylating agent employed in place of α,α' -dibromo-*p*-xylene, using the same molar proportions as before. In the particular case, the corresponding final prod-

EP 0 252 713 B1

uct obtained was 1'-acetyl-5(6)-chloro-1,2-dihydro-spiro-inden[2,3']indolin-2'-one, m.p. 108-110°C. after recrystallization from aqueous N,N-dimethylformamide. The yield of pure product was 57% of the theoretical value.

5 PREPARATION T

A stirred mixture consisting of 760 mg. (0.0158 mole) of pentane-washed sodium hydride (50% oil dispersion) and 100 ml. of dry N,N-dimethylformamide was treated under a dry nitrogen atmosphere with 5.5 g. (0.0158 mole) of N-acetyl-3-(3,4-dichloro--methylbenzyl)-2-indolinone (the product of Preparation P) dissolved in 50 ml. of dry N,N-dimethylformamide. The latter solution was added over the course of a two-minute period and when the addition was complete, the resulting mixture was stirred at room temperature (~20°C.) for a period of 30 minutes to give a dark brown solution. At this point, 1.0 ml. (0.016 mole) of methyl iodide was added and the final reaction mixture was stirred at room temperature for a period of 18 hours. Upon completion of this step, the resulting organic solution was poured onto 200 ml. of ice/water and stirred for a period of one hour, followed by extraction with diethyl ether. The ethereal extract was thereafter washed with water and brine, and finally dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a yellow residual oil which consisted of 4.05 g. (71%) of pure 1-acetyl-3-(3,4-dichloro--methylbenzyl)-3-methyl-2-indolinone. The pure product was characterized by means of mass spectroscopy, nuclear magnetic resonance and thin layer chromatography.

PREPARATION U

A mixture consisting of 5.0 g. (0.0306 mole) of N-acetyl-2-indolinone (the product of Preparation O), 9.8 g. (0.0708 mole) of potassium carbonate and 11.6 g. (0.070 mole) of potassium iodide in 80 ml. of N,N-dimethylformamide was stirred under a dry nitrogen atmosphere at room temperature (~20°C.), while a solution consisting of 8.9 ml. (0.0643 mole) of 3,4-dichlorobenzyl chloride dissolved in 20 ml. of N,N-dimethylformamide was slowly added thereto. The resulting reaction mixture was then stirred at room temperature for a period of 72 hours and finally partitioned between water and diethyl ether. The aqueous layer was then extracted twice with diethyl ether, and the combined organic layers were subsequently washed once with water and once with brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a pale pink solid as the residue. Recrystallization of the latter material from aqueous N,N-dimethylformamide then gave 5.75 g. (38%) of pure 1-acetyl-3,3-di(3,4-dichlorobenzyl)-2-indolinone monohydrate, m.p. 177-179°C. after first drying to constant weight in vacuo for a period of approximately 16 hours (i.e., overnight). The pure product was further characterized by means of mass spectroscopy, nuclear magnetic resonance data and thin layer chromatography, in addition to elemental analysis.

Anal. Calcd. for $C_{24}H_{17}NO_2Cl_4 \cdot H_2O$: C, 56.38; H, 3.75; N, 2.74. Found: C, 56.43; H, 3.52; N, 2.80.

40 PREPARATION V

A mixture consisting of 7.4 g. (0.0267 mole) of 1'-acetyl-1,2-dihydro-spiro-inden[2,3']indolin-2'-one semihydrate (the product of Preparation Q) in 170 ml. of 4% aqueous sodium hydroxide and 170 ml. of absolute methanol was stirred and heated on a steam bath for a period of 30 minutes. Upon completion of this step, the resulting solution was cooled to 25°C. and then acidified to pH 2 with concentrated hydrochloric acid. After removal of excess methanol by means of evaporation under reduced pressure, the resulting solids were filtered, washed with water and dried in vacuo to constant weight to ultimately afford 5.65 g. (90%) of pure 1,2-dihydro-spiro-inden[2,3']indolin-2'-one semihydrate, m.p. 186-189°C. Recrystallization of the latter material from aqueous methanol did not change value of the melting point. The mass spectrum was m/e 235.

Anal. Calcd. for $C_{16}H_{13}NO \cdot 0.5H_2O$: C, 78.66; H, 5.78; N, 5.74. Found: C, 78.96; H, 5.64; N, 5.74.

55 PREPARATION W

The procedure described in Preparation V was repeated except that 1'-acetyl-5(6)-chloro-1,2-dihydro-spiro-inden[2,3']indolin-2'-one (the product of Preparation S) was the starting material employed in place of 1'-acetyl-1,2-dihydro-spiro-inden[2,3']indolin-2'-one semihydrate, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 5(6)-chloro-1,2-dihydro-spiro-inden[2,3']indolin-2'-one, m.p. 160-163°C. (decomp.). The yield of pure product was 61% of the theoretical value.

PREPARATION X

65 The procedure described in Preparation V was repeated except that 1-acetyl-3,3-di(3,4-dichloroben-

EP 0 252 713 B1

5 zyl)-2-indolinone monohydrate (the product of Preparation U) was the starting material employed in place of 1'-acetyl-1,2-dihydro-~~spiro~~-inden[2,3']-indolin-2'-one, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3,3-di(3,4-dichlorobenzyl)-2-indolinone, m.p. 165-170°C. after recrystallization from aqueous methanol. The yield of pure product was 87% of the theoretical value.

PREPARATION Y

10 A mixture consisting of 4.0 g. (0.011 mole) of 1-acetyl-3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-indolinone (the product of Preparation T) in 70 ml. of 4% aqueous sodium hydroxide and 70 ml. of absolute methanol was stirred and heated on a steam bath for a period of one hour. At this point, an additional 40 ml. of 4% aqueous sodium hydroxide was added to the mixture, followed by continued refluxing on the steam bath for a further period of three hours. Upon completion of this step, the resulting reaction solution was stirred at room temperature (-20°C.) for approximately 18 hours (overnight) and then acidified to pH 1.0 with 6N hydrochloric acid. Extraction of the product was next accomplished with three-100 ml. portions of methylene chloride, and the combined organic layers were subsequently washed with water and brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there were obtained 3.41 g. (97%) of pure 3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-indolinone in the form of a yellow gum. The pure product was characterized by means of mass spectroscopy, nuclear magnetic resonance data and thin layer chromatography.

PREPARATION Z

25 The procedure described in Preparation G was repeated except that 1,2-dihydro-indene[2,3']indolin-2'-one semihydrate (the product of Preparation V) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 1,2-dihydro~~spiro~~-inden[2,3']indolin-2'-one-1'-acetic acid benzyl ester semihydrate, m.p. 141-143°C. after recrystallization from aqueous N,N-dimethylformamide. The yield of pure product was 93% of the theoretical value.

PREPARATION AA

35 The procedure described in Preparation G was repeated except that 5(6)-chloro-1,2-dihydro-~~spiro~~-inden[2,3']indolin-2'-one (the product of Preparation W) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 5(6)-chloro-1,2-dihydro-~~spiro~~-inden[2,3']indolin-2'-one-1'-acetic acid benzyl ester, m.p. 136-140°C. after recrystallization from chloroform. The yield of pure product was 48% of the theoretical value.

PREPARATION BB

45 The procedure described in Preparation G was repeated except that 3,3-di(3,4-dichlorobenzyl)-2-indolinone (the product of Preparation X) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3,3-di(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid benzyl ester (obtained as an oil). The yield of pure product was 48% of the theoretical value.

PREPARATION CC

50 The procedure described in Preparation G was repeated except that 3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-indolinone (the product of Preparation Y) was the starting material employed in place of 3-(3,4-dichlorobenzylidene)-2-indolinone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was 3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-oxo-indoline-1-acetic acid benzyl ester (obtained as an oil). The yield of pure product was 79% of the theoretical value.

EXAMPLE 1

60 A suspension consisting of 2.28 g. (0.0052 mole) of ~~dis~~-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester as the semihydrate (the product of Preparation G) and 1.0 g. of 5% palladium-on-carbon catalyst in 50 ml. of ethyl acetate containing 2 ml. of glacial acetic acid was hydrogenated at atmospheric pressure until the uptake of hydrogen gas ceased (~3 hours). Thin layer chromatography analysis, using chloroform/methanol (9:1 by volume) as the eluant, showed no benzyl ester present at

EP 0 252 713 B1

this point and revealed a single product at $R_f=0.50$. The reaction solution was then filtered through Celite (diatomaceous earth) to remove the catalyst, and the resulting filtrate was subsequently concentrated in vacuo to a pale yellow foam. Recrystallization of the latter material from aqueous ethanol then gave a white solid product consisting of 1.325 g. (73%) of pure 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, m.p. 168-171°C.; mass spectrum, m/e 351/349.

Anal. Calcd. for $C_{17}H_{13}NO_3Cl_2$: C, 58.30; H, 3.74; N, 4.00. Found: C, 58.54; H, 3.88; N, 3.91.

EXAMPLE 2

The hydrogenolysis procedure described in Example 1 was repeated except that 5-chloro-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester as the quarter-hydrate (the product of Preparation H) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 5-chloro-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid isolated as the dicyclohexylamine salt, m.p. 148-150°C. after recrystallization from ethanol/diethyl ether. The yield of pure product was 18% of the theoretical value.

EXAMPLE 3

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichlorobenzylidene)-6-fluoro-2-oxo-indoline-1-acetic acid benzyl ester as the quarter-hydrate (the product of Preparation I) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzyl)-6-fluoro-2-oxo-indoline-1-acetic acid, isolated as the dicyclohexylamine salt, m.p. 157-160°C. (decomp.) after recrystallization from diethyl ether/pentane. The yield of pure product was 28% of the theoretical value.

EXAMPLE 4

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichlorobenzylidene)-5,6-dimethoxy-2-oxo-indoline-1-acetic acid benzyl ester (the product of Preparation J) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzyl)-5,6-dimethoxy-2-oxo-indoline-1-acetic acid, isolated as the dicyclohexylamine salt, m.p. 222-223°C. (decomp.) after recrystallization from diethyl ether. The yield of pure product was 17% of the theoretical value.

EXAMPLE 5

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichlorobenzylidene)-6-methoxy-2-oxo-indoline-1-acetic acid benzyl ester (the product of Preparation K) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzyl)-6-methoxy-2-oxo-indoline-1-acetic acid, isolated as the dicyclohexylamine salt, m.p. 182-183°C. after recrystallization from diethyl ether. The yield of pure product was 81% of the theoretical value.

EXAMPLE 6

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-(α -methyl)acetic acid benzyl ester (the product of Preparation L) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-(α -methyl)acetic acid, isolated as the semihydrate of the dicyclohexylamine salt, m.p. 94-96°C. (decomp.) The yield of pure product was 57% of the theoretical value.

EXAMPLE 7

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichloro- α -methylbenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester (the product of Preparation M) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichloro- α -methylbenzyl)-2-oxo-indoline-1-acetic acid, m.p. 175-177°C. (decomp.) after recrystallization from aqueous ethanol. The yield of pure product was 50% of the theoretical value.

EP 0 252 713 B1

EXAMPLE 8

The hydrogenolysis procedure described in Example 1 was repeated except that the semihydrate of 1,2-dihydro-spiro-inden[2,3']indolin-2'-one-1'-acetic acid benzyl ester (the product of Preparation Z) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 1,2-dihydro-spiro-inden[2,3']indolin-2'-one-1'-acetic acid, isolated as the dicyclohexylamine salt, m.p. 185-187°C. after recrystallization from ethanol/diethyl ether. The yield of pure product was 13% of the theoretical value.

EXAMPLE 9

The hydrogenolysis procedure described in Example 1 was repeated except that 5(6)-chloro-1,2-dihydro-spiro-inden[2,3']indolin-2'-one-1'-acetic acid benzyl ester (product of Preparation AA) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 5(6)-chloro-1,2-dihydro-spiro-inden[2,3']indolin-2'-one-1'-acetic acid, isolated as the dicyclohexylamine salt, m.p. 135-136°C. (decomp.) after recrystallization from ethanol/pentane. The yield of pure product was 89% of the theoretical value.

EXAMPLE 10

The hydrogenolysis procedure described in Example 1 was repeated except that 3,4-di(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid benzyl ester (the product of Preparation BB) was the starting material employed in place of the semihydrate of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3,3-di(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid, isolated as the dicyclohexylamine salt, m.p. 185-186°C. after recrystallization from diethylether/pentane. The yield of pure product was 65% of the theoretical value.

EXAMPLE 11

The hydrogenolysis procedure described in Example 1 was repeated except that 3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-oxo-indoline-1-acetic acid benzyl ester (the product of Preparation CC) was the starting material employed in place of cis-3-(3,4-dichlorobenzylidene)-2-oxo-indoline-1-acetic acid benzyl ester. In this particular case, the corresponding final product obtained was 3-(3,4-dichloro- α -methylbenzyl)-3-methyl-2-oxo-indoline-1-acetic acid, isolated as the dicyclohexylamine salt, m.p. 151-153°C. after recrystallization from diethyl ether. The yield of pure product was 72% of the theoretical value.

EXAMPLE 12

A solution consisting of 1.8 g. (0.0473 mole) of 3-(3,4-dichlorobenzyl)-6-methoxy-2-oxo-indoline-1-acetic acid as the dicyclohexylamine salt (the product of Example 5) dissolved in 60 ml. of methylene chloride was cooled to 0°C. while under a nitrogen atmosphere and treated with 9.5 ml. (0.095 mole) of 1M boron tribromide in methylene chloride, which was added in a dropwise manner over a period of 1.5 minutes. Upon completion of this step, the resulting reaction mixture was stirred for a period of 15 minutes and then allowed to warm to 25°C. over a period of one hour to give a clear red solution. At this point, another 10 ml. portion of 1M boron tribromide in methylene chloride was added to the mixture, which was then stirred overnight (~18 hours) at 25°C. and subsequently poured over 100 ml. of ice water. The product thus obtained was then extracted from the aqueous layer, first with methylene chloride and then with ethyl acetate, and the combined organic layers were subsequently washed once with water and once with brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a viscous oil (yield, 1.7 g.) as the residue. The latter material was subsequently dissolved in 150 ml. of anhydrous diethyl ether and treated with 2.4 ml. (~2.5 equivalents) of dicyclohexylamine and then allowed to crystallize. In this way, there was readily obtained the corresponding crystalline dicyclohexylamine salt, which was thereafter recovered by means of filtration, washed with diethyl ether and pentane, and then dried in vacuo to constant weight to ultimately afford 1.7 g. (65%) of pure 3-(3,4-dichlorobenzyl)-6-hydroxy-2-oxo-indoline-1-acetic acid (as the dicyclohexylamine salt), m.p. 141-144°C. (decomp.). Recrystallization of the latter material from diethyl ether did not raise the melting point.

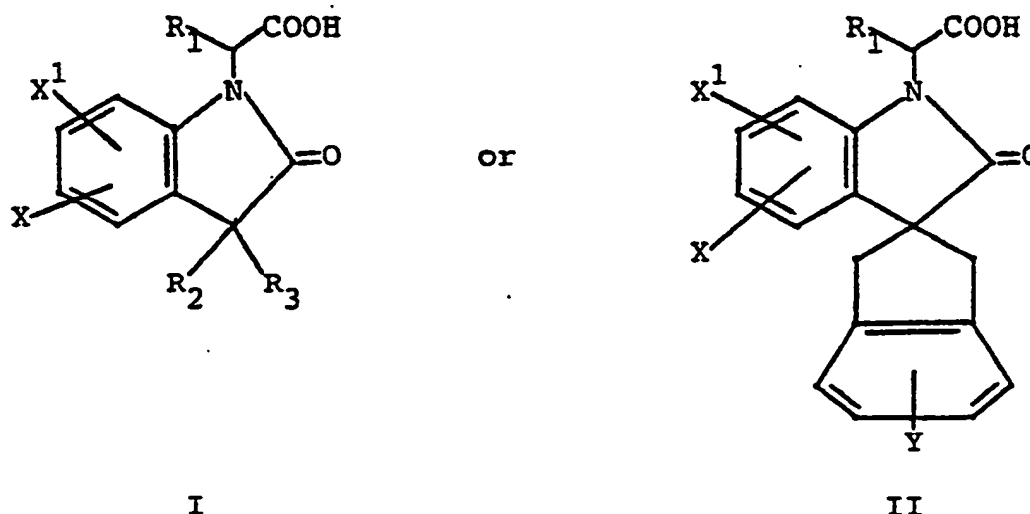
EXAMPLE 13

The following oxindole-1-alkanoic acid final products of Examples 1-12, respectively, were tested at a

concentration level of 10^{-5}M for their ability to reduce or inhibit aldose reductase enzyme activity via the procedure of S. Hayman et al., as described in the Journal of Biological Chemistry, Vol. 240, p. 877 (1965) and as modified by K. Sestanji et al. in U.S. Patent No. 3,821,383. In every case, the substrate employed was partially purified aldose reductase enzyme obtained from human placenta. The results obtained with each compound are expressed below in terms of their percent inhibition of enzyme activity (%) with respect to the particular concentration level chosen (10^{-5}M):

Compound	% Inhibition at 10^{-5} M
Product of Example 1	92
Product of Example 2	88
Product of Example 3	68
Product of Example 4	55
Product of Example 5	81
Product of Example 6	25
Product of Example 7	94
Product of Example 8	66
Product of Example 9	71
Product of Example 10	20
Product of Example 11	72
Product of Example 12	79

1. An oxindole-1-alkanoic acid compound of the formula:



X is hydrogen and X' is hydrogen, hydroxy, fluoro, chlorine, bromine, C₁-C₄ alkyl or C₁-C₄ alkoxy; or X and X', when taken separately, are each chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy, and when taken together are -OCH₂(CH₂)_nO- at the 4,5-, 5,6- or 6,7-positions of the molecule wherein n is zero or one;

R₂ is hydrogen, C₁-C₄ alkyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two chlorine substituents on the phenyl ring;

R₃ is naphthylmethyl, furfuryl, thenyl, benzothienylmethyl, benzoxazolylmethyl, benzothiazolylmethyl or

EP 0 252 713 B1

phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two identical or non-identical substituents on the phenyl ring, said identical substituents being fluorine, chlorine, bromine, trifluoromethyl, C₁-C₄ alkyl or C₁-C₄ alkoxy and said non-identical substituents being chlorine, methyl, methoxy or trifluoromethyl; and

5 Y is hydrogen, fluorine, chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy.

2. A compound as claimed in claim 1 of the formula I wherein X is hydrogen and X¹ is hydrogen, hydroxy, fluorine, chlorine or C₁-C₄ alkoxy; X and X¹, when taken separately, are each C₁-C₄ alkoxy; R₁ is hydrogen or methyl; and R₂ and R₃ are each hydrogen, C₁-C₄ alkyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is ring-substituted with up to two chlorine atoms on the phenyl ring.

3. A compound as claimed in claim 2 wherein X is hydrogen and X¹ is hydrogen, hydroxy, chlorine or methoxy; R₁ and R₂ each hydrogen, and R₃ is 3,4-dichlorobenzyl or 3,4-dichloro- α -methylbenzyl.

4. A compound as claimed in claim 3 wherein X¹ is hydrogen.

5. A compound as claimed in claim 3 wherein X¹ is hydroxy at the 6-position of the molecule and R₃ is 3,4-dichlorobenzyl.

6. A compound as claimed in claim 3 wherein X¹ is chlorine at the 5-position of the molecule and R₃ is 3,4-dichlorobenzyl.

7. A compound as claimed in claim 3 wherein X¹ is methoxy at the 6-position of the molecule and R₃ is 3,4-dichlorobenzyl.

8. A compound as claimed in claim 1 of the formula II wherein X is hydrogen and X¹ is hydrogen, hydroxy, chlorine or methoxy; R₁ is hydrogen, and Y is hydrogen, hydroxy, chlorine or methoxy.

9. A compound as claimed in claim 8 wherein X¹ is hydrogen and Y is hydrogen or chlorine at the 5(6)-position of the molecule.

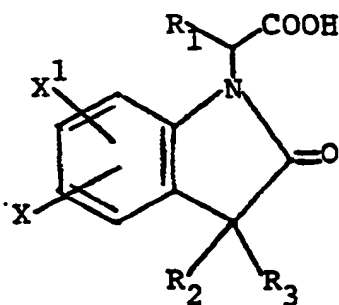
10. A pharmaceutical composition suitable for oral administration comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount effective for the treatment of diabetes-associated chronic complications.

11. A compound as claimed in any one of claims 1 to 9 for use as a medicament.

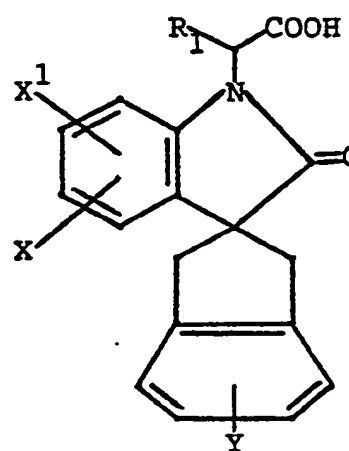
12. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for treating diabetes-associated chronic complications.

30 **Claims for the following Contracting States: AT; GR; ES**

1. A process for preparing a 3-substituted 2-oxo-indoline-1-alkanoic acid compound of the formula:



or



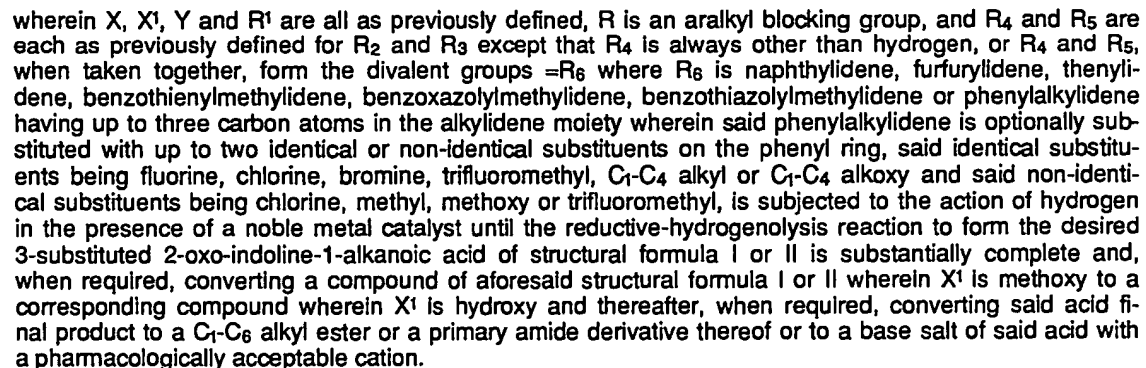
I

II

55 or a C₁-C₆ alkyl ester or a primary amide derivative thereof, or a base salt of said acid with a pharmacologically acceptable cation, wherein X is hydrogen and X¹ is hydrogen, hydroxy, fluorine, chlorine, bromine, C₁-C₄ alkyl or C₁-C₄ alkoxy; or X and X¹, when taken separately, are each chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy, and when taken together are -OCH₂(CH₂)_nO- at the 4,5-, 5,6- or 6,7-positions of the molecule wherein n is zero or one; R₁ is hydrogen or methyl; R₂ is hydrogen, C₁-C₄ alkyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two chlorine substituents on the phenyl ring; R₃ is naphthylmethyl, furfuryl, thenyl, benzothienylmethyl, benzoxazolylmethyl, benzothiazolylmethyl or phenylalkyl having up to three carbon atoms in the alkyl moiety wherein said phenylalkyl is optionally substituted with up to two identical or non-identical sub-

65

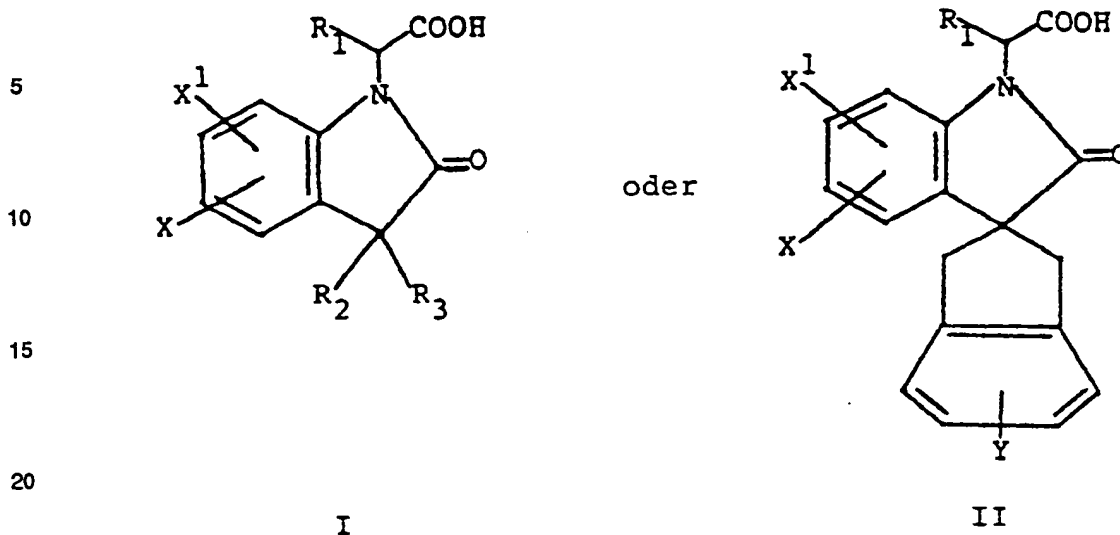
stituents on the phenyl ring, said identical substituents being fluorine, chlorine, bromine, trifluoromethyl, C₁-C₄ alkyl or C₁-C₄ alkoxy and said non-identical substituents being chlorine, methyl, methoxy or trifluoromethyl; and Y is hydrogen, fluorine, chlorine, C₁-C₄ alkyl or C₁-C₄ alkoxy, characterized by subjecting an appropriately substituted 2-oxo-indoline-1-alkanoic acid aralkyl ester of the formula:



10. A process as claimed in claim 1 wherein the compound prepared is 6-hydroxy-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acetic acid.

1. Oxindol-1-alkansäure-Verbindung mit der Formel

EP 0 252 713 B1



25 oder ein C₁-C₈-Alkylester- oder primäres Amid-Derivat hiervon oder ein Basen-Salz dieser Säure mit einem pharmakologisch annehmbaren Kation, worin X Wasserstoff bedeutet und X¹ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy ist, oder worin X und X¹, wenn sie einzelne Gruppen darstellen, jeweils Chlor, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy bedeuten, und dann, wenn sie zusammen eine Gruppe bilden, in 4,5-, 5,6- oder 6,7-Stellung des Moleküls -OCH₂(CH₂)_nO- darstellen, wobei n null oder eins bedeutet,

30 R₁ Wasserstoff oder Methyl darstellt,

R₂ Wasserstoff, C₁-C₄-Alkyl oder Phenylalkyl mit bis zu drei Kohlenstoffatomen in der Alkylgruppe ist, wobei dieses Phenylalkyl fakultativ mit bis zu zwei Chlor-Substituenten am Phenylring substituiert ist,

35 R₃ Naphthylmethyl, Furfuryl, Thenyl, Benzothienylmethyl, Benzoxazolylmethyl, Benzothiazolylmethyl oder Phenylalkyl mit bis zu drei Kohlenstoffatomen in der Alkylgruppe ist, wobei dieses Phenylalkyl am Phenylring fakultativ mit bis zu zwei identischen oder nicht identischen Substituenten substituiert ist, wobei die identischen Substituenten Fluor, Chlor, Brom, Trifluormethyl, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy sind und die nicht identischen Substituenten Chlor, Methyl, Methoxy oder Trifluormethyl sind, und Y Wasserstoff, Fluor, Chlor, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy ist.

40 2. Verbindung nach Anspruch 1 mit der Formel I, worin X Wasserstoff ist und X¹ Wasserstoff, Hydroxy, Fluor, Chlor oder C₁-C₄-Alkoxy ist, X und X¹, wenn sie einzelne Gruppen darstellen, jeweils C₁-C₄-Alkoxy sind, R₁ Wasserstoff oder Methyl bedeutet und R₂ und R₃ jeweils Wasserstoff, C₁-C₄-Alkyl oder Phenylalkyl mit bis zu drei Kohlenstoffatomen in der Alkylgruppe darstellen, wobei das genannte Phenylalkyl mit bis zu zwei Chloratomen am Phenylring ringsubstituiert ist.

45 3. Verbindung nach Anspruch 2, worin X Wasserstoff ist und X¹ Wasserstoff, Hydroxy, Chlor oder Methoxy bedeutet, R₁ und R₂ jeweils Wasserstoff sind und R₃ 3,4-Dichlorbenzyl oder 3,4-Dichlor-alpha-methylbenzyl ist.

4. Verbindung nach Anspruch 3, worin X¹ Wasserstoff ist.

5. Verbindung nach Anspruch 3, worin X¹ Hydroxy in 6-Stellung des Moleküls ist und R₃ 3,4-Dichlorbenzyl ist.

50 6. Verbindung nach Anspruch 3, worin X¹ Chlor in 5-Stellung des Moleküls ist und R₃ 3,4-Dichlorbenzyl ist.

7. Verbindung nach Anspruch 3, worin X¹ Methoxy in 6-Stellung des Moleküls ist und R₃ 3,4-Dichlorbenzyl ist.

55 8. Verbindung nach Anspruch 1 mit der Formel II, worin X Wasserstoff ist und X¹ Wasserstoff, Hydroxy, Chlor oder Methoxy bedeutet, R₁ Wasserstoff ist und Y Wasserstoff, Hydroxy, Chlor oder Methoxy ist.

9. Verbindung nach Anspruch 8, worin X¹ Wasserstoff ist und Y Wasserstoff oder Chlor in 5(6)-Stellung des Moleküls ist.

60 10. Pharmazeutische Zusammensetzung, die sich für die orale Verabreichung eignet, enthaltend einen pharmazeutisch annehmbaren Träger und eine Verbindung nach Anspruch 1 in einer Menge, die für die Behandlung von mit Diabetes assoziierten chronischen Komplikationen wirksam ist.

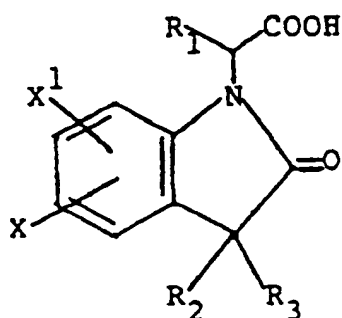
11. Verbindung nach einem der Ansprüche 1 bis 9 für die Verwendung als Medikament.

65 12. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 9 für die Herstellung eines Medikaments für die Behandlung von mit Diabetes assoziierten chronischen Komplikationen.

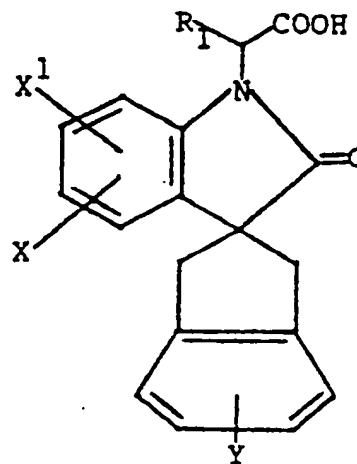
EP 0 252 713 B1

Patentansprüche für die Vertragsstaaten: AT, GR, ES

1. Verfahren zum Herstellen einer 3-substituierten 2-Oxoindolin-1-alkansäure-Verbindung mit der Formel



oder



I

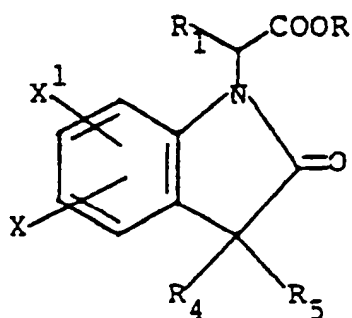
II

oder eines C₁-C₆-Alkylester- oder primären Amid-Derivates hiervon oder eines Basen-Salzes dieser Säure mit einem pharmakologisch annehmbaren Kation, worin X Wasserstoff bedeutet und X¹ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy ist, oder worin X und X¹, wenn sie einzelne Gruppen darstellen, jeweils Chlor, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy bedeuten, und dann, wenn sie zusammen eine Gruppe bilden, in 4,5-, 5,6- oder 6,7-Stellung des Moleküls -OCH₂(CH₂)_nO darstellen, wobei n null oder eins bedeutet,

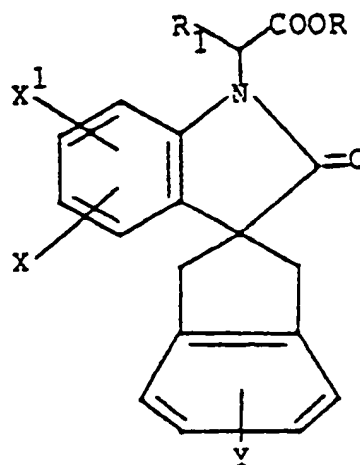
R¹ Wasserstoff oder Methyl darstellt,

R² Wasserstoff, C₁-C₄-Alkyl oder Phenylalkyl mit bis zu drei Kohlenstoffatomen in der Alkylgruppe ist, wobei dieses Phenylalkyl fakultativ mit bis zu zwei Chlor-Substituenten am Phenylring substituiert ist,

R³ Naphthylmethyl, Furfuryl, Thenyl, Benzothienylmethyl, Benzoxazolylmethyl, Benzothiazolylmethyl oder Phenylalkyl mit bis zu drei Kohlenstoffatomen in der Alkylgruppe ist, wobei dieses Phenylalkyl am Phenylring fakultativ mit bis zu zwei identischen oder nicht identischen Substituenten substituiert ist, wobei die identischen Substituenten Fluor, Chlor, Brom, Trifluormethyl, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy sind und die nicht identischen Substituenten Chlor, Methyl, Methoxy oder Trifluormethyl sind, und Y Wasserstoff, Fluor, Chlor, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy ist, dadurch gekennzeichnet, daß man einen geeignet substituierten 2-Oxo-indolin-1-alkansäure-aralkylester mit der Formel:



oder



III

IV

EP 0 252 713 B1

worin X, X¹, Y und R¹ jeweils wie voranstehend definiert sind, R eine Aralkyl-Blockierungsgruppe ist und R₄ und R₅ jeweils die wie vorstehend für R₂ und R₃ gegebene Definition besitzen, mit der Änderung, daß R₄ immer eine andere Bedeutung als Wasserstoff hat, oder R₄ und R₅, wenn sie zusammen eine Gruppe bilden, die divalente Gruppe R₆ bilden, wobei R₆ Naphthyliden, Furfuryliden, Thienyliden, Benzothienylmethyliden, Benzoxazolylmethyliden, Benzothiazolylmethyliden oder Phenylalkyliden mit bis zu drei Kohlenstoffatomen in der Alkyliden-Gruppe darstellt, wobei dieses Phenylalkyliden fakultativ mit bis zu zwei identischen oder nicht identischen Substituenten am Phenylring ringsubstituiert ist, wobei die identischen Substituenten Fluor, Chlor, Brom, Trifluomethyl, C₁-C₄-Alkyl oder C₁-C₄-Alkoxy sind und die nicht identischen Substituenten Chlor, Methyl, Methoxy oder Trifluomethyl sind, in Gegenwart eines Edelmetallkatalysators der Einwirkung von Wasserstoff unterwirft, bis die reduktive Hydrogenolyse-Reaktion zur gewünschten 3-substituierten 2-Oxo-indolin-1-alkansäure mit der Strukturformel I oder II im wesentlichen vollständig ist, und, wenn erforderlich, die Verbindung der vorgenannten Strukturformel I oder II, worin X¹ Methoxy bedeutet, in eine entsprechende Verbindung überführt, worin X¹ Hydroxy bedeutet, und danach, wenn erforderlich, dieses Säure-Endprodukt in ein C₁-C₆-Alkylester- oder primäres Amid-Derivat davon oder in ein Basensalz dieser Säure mit einem pharmakologisch annehmbaren Kation überführt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Aralkyl-Blockierungsgruppe von R in der Ausgangssubstanz mit der Strukturformel III oder IV Benzyl ist.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß der für die Reaktion eingesetzte Edelmetallkatalysator Palladium auf Kohle ist.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Umsetzung in einem reaktionsinerten organischen Solvens in Gegenwart einer kleineren Menge an Säure durchgeführt wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Umsetzung in einem Druckbereich von 103, 4 bis 344, 7 kPa (15 bis 50 psi) Wasserstoff und bei einer Temperatur durchgeführt wird, die im Bereich von etwa 0°C bis hin zu etwa 50°C liegt.

6. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3-(3,4-Dichlorbenzyl)-2-oxo-indolin-1-essigsäure ist.

7. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3-(3,4-Dichlor-alpha-methylbenzyl)-2-oxo-indolin-1-essigsäure ist.

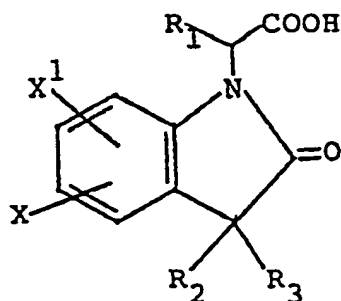
8. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 5-Chlor-3-(3,4-dichlorbenzyl)-2-oxo-indolin-1-essigsäure ist.

9. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 6-Methoxy-3-(3,4-dichlorbenzyl)-2-oxo-indolin-1-essigsäure ist.

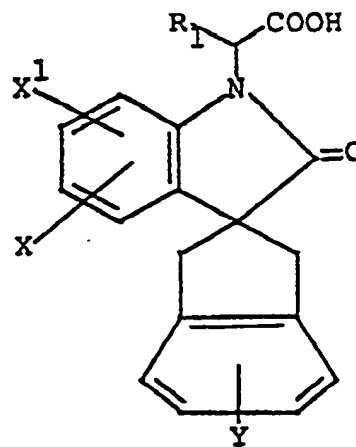
10. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 6-Hydroxy-3-(3,4-dichlorbenzyl)-2-oxo-indolin-1-essigsäure ist.

Revendications pour les etats contractants: BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Composé d'acide oxindole-1-alkanoïque de formules:



ou



I

II

ou ester d'alkyle en C₁-C₆ ou dérivé amide primaire d'un tel composé, ou sel de base dudit acide avec un cation pharmaceutiquement acceptable, formules dans lesquelles:

EP 0 252 713 B1

X représente l'hydrogène et X' représente l'hydrogène, un groupe hydroxy, fluoro, chloro, bromo, alkyle en C₁-C₄ ou alcoxy en C₁-C₄; ou

X et X', lorsqu'ils sont pris séparément, sont identiques ou différents et représentent un radical chloro, alkyle en C₁-C₄ ou alcoxy en C₁-C₄ et, lorsqu'il sont pris ensemble, représentent une chaîne -OCH₂(CH₂)_n- en positions 4,5-, 5,6-, ou 6,7- de la molécule, n représentant zéro ou un;

R₁ représente l'hydrogène ou un groupe méthyle;

R₂ représente l'hydrogène, un groupe alkyle en C₁-C₄ ou phénylalkyle ayant jusqu'à trois atomes de carbone dans la partie alkyle, ledit groupe phénylalkyle étant éventuellement substitué par jusqu'à deux substituants chloro sur le noyau phényle;

R₃ est un radical naphthylméthyle, furfuryle, thényle, benzothiénylméthyle, benzoxazolyméthyle, benzothiazolyméthyle ou phénylalkyle ayant jusqu'à trois atomes de carbone dans la partie alkyle, ledit groupe phénylalkyle étant éventuellement substitué par jusqu'à deux substituants identiques ou non sur le noyau phényle, lesdits substituants identiques étant des groupes fluoro, chloro, bromo, trifluorométhyle, alkyle en C₁-C₄ ou alcoxy en C₁-C₄ et lesdits substituants non identiques étant des radicaux chloro, méthyle, méthoxy ou trifluorométhyle; et

Y représente l'hydrogène, un radical fluoro, chloro, alkyle en C₁-C₄ ou alcoxy en C₁-C₄.

2. Composé selon la revendication 1 de formule I dans laquelle X représente l'hydrogène et X' représente l'hydrogène, un groupe hydroxy, fluoro, chloro ou un groupe alcoxy en C₁-C₄; X et X', lorsqu'ils sont pris séparément, représentent chacun un groupe alcoxy en C₁-C₄; R₁ représente l'hydrogène ou un groupe méthyle; R₂ et R₃ représentent chacun l'hydrogène, un groupe alkyle en C₁-C₄ ou phénylalkyle ayant jusqu'à trois atomes de carbone dans la partie alkyle, ledit groupe phénylalkyle étant substitué sur le cycle phényle par jusqu'à deux atomes de chloro.

3. Composé selon la revendication 2 dans lequel X représente l'hydrogène et X' représente l'hydrogène, un groupe hydroxy, chloro ou méthoxy; R₁ et R₂ représentent chacun l'hydrogène et R₃ est un groupe 3,4-dichloro- α -benzyle ou 3,4-dichloro- α -méthylbenzyle.

4. Composé selon la revendication 3 dans lequel X' représente l'hydrogène.

5. Composé selon la revendication 3 dans lequel X' est un groupe hydroxy en position-6 de la molécule et R₃ est un groupe 3,4-dichlorobenzyle.

6. Composé selon la revendication 3, dans lequel X' représente un radical chloro en position-5 de la molécule et R₃ est un groupe 3,4-dichlorobenzyle.

7. Composé selon la revendication 3, dans lequel X' est un groupe méthoxy en position-6 de la molécule et R₃ est un groupe 3,4-dichlorobenzyle.

8. Composé selon la revendication 1 de formule II dans laquelle X représente l'hydrogène et X' représente l'hydrogène, un groupe hydroxy, chloro ou méthoxy; R₁ représente l'hydrogène et Y représente l'hydrogène, un groupe hydroxy, chloro ou méthoxy.

9. Composé selon la revendication 8, dans lequel X' représente l'hydrogène et Y représente l'hydrogène ou un groupe chloro en position-5(6) de la molécule.

10. Composition pharmaceutique convenant à l'administration orale comprenant un support pharmaceutiquement acceptable et un composé selon la revendication 1 en quantité efficace pour le traitement des complications chroniques associées au diabète.

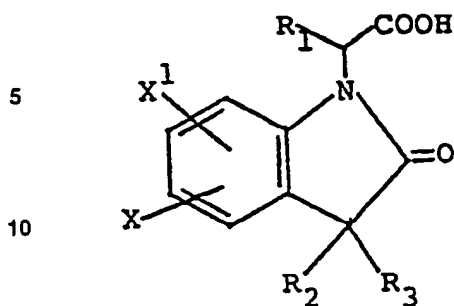
11. Composé selon l'une quelconque des revendications 1 à 9, pour son utilisation comme médicament.

12. Utilisation du composé selon l'une quelconque des revendications 1 à 9, pour la fabrication d'un médicament destiné au traitement des complications chroniques associées au diabète.

Revendications pour les états contractants: AT, GR, ES

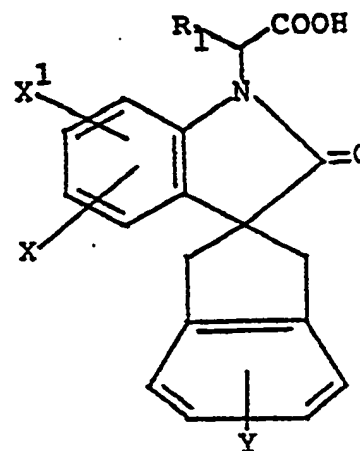
1. Procédé de préparation d'un composé acide 2-oxoindoline-1-alconoïque-3-substitué de formules:

EP 0 252 713 B1



I

ou



II

d'un ester d'alkyle en C₁-C₆ ou d'un dérivé amide primaire d'un tel composé, ou d'un sel de base dudit acide avec un cation pharmacologiquement acceptable, formules dans lesquelles:

X représente l'hydrogène et X¹ représente l'hydrogène, un groupe hydroxy, fluoro, chloro, bromo, alkyle en C₁-C₄ ou alcoxy en C₁-C₄; ou

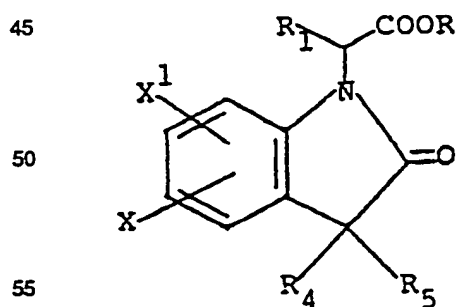
X et X¹, lorsqu'ils sont pris séparément, sont identiques ou différents et représentent un radical chloro, alkyle en C₁-C₄ ou alcoxy en C₁-C₄ et, lorsqu'ils sont pris ensemble, représentent une chaîne -OCH₂(CH₂)_nO- en positions 4,5-, 5,6-, ou 6,7- de la molécule, n représentant zéro ou un;

R₁ représente l'hydrogène ou un groupe méthyle;

R₂ représente l'hydrogène, un groupe alkyle en C₁-C₄ ou phénylalkyle ayant jusqu'à trois atomes de carbone dans la partie alkyle, ledit groupe phénylalkyle étant éventuellement substitué par jusqu'à deux substituants chloro sur le noyau phényle;

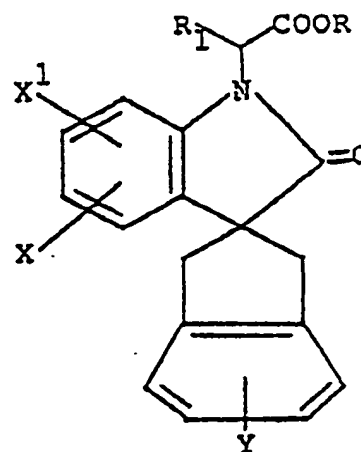
R₃ est un radical naphthylméthyle, furfuryle, thényle, benzothiénylméthyle, benzoxazolylméthyle, benzothiazolylméthyle ou phénylalkyle ayant jusqu'à trois atomes de carbone dans la partie alkyle, ledit groupe phénylalkyle étant éventuellement substitué par jusqu'à deux substituants identiques ou non sur le noyau phényle, lesdits substituants identiques étant des groupes fluoro, chloro, bromo, trifluorométhyle, alkyle en C₁-C₄ ou alcoxy en C₁-C₄ et lesdits substituants non identiques étant des radicaux chloro, méthyle, méthoxy ou trifluorométhyle.; et

Y représente l'hydrogène, un radical fluoro, chloro, alkyle en C₁-C₄ ou alcoxy en C₁-C₄, caractérisé en ce qu'il consiste à soumettre un ester d'aralkyle de l'acide 2-oxo-indoline-1-alcanoïque convenablement substitué de formules:



III

ou



IV

EP 0 252 713 B1

dans lesquelles X, X¹, Y et R₁ sont tels que précédemment définis, R est un groupe de blocage aralkyle et R₄ et R₅ sont chacun comme précédemment définis pour R₂ et R₃ excepté que R₄ est toujours différent de l'hydrogène, ou R₄ et R₅, lorsqu'ils sont pris ensemble, forment des groupes divalents =R₆ où R₆ est un groupe naphtylidène, furfurylidène, thénylidène, benzothiénylméthylidène, benzoxazolyméthylidène, benzothiazolyméthylidène, ou phénylalkylidène ayant jusqu'à trois atomes de carbone dans la partie alkylidène, ledit groupe phénylalkylidène étant éventuellement substitué par jusqu'à deux substituants identiques ou non sur le noyau phényle, lesdits substituants identiques étant des radicaux fluoro, chloro, bromo, trifluorométhyle, alkyle en C₁-C₄ ou alcoxy en C₁-C₄ et lesdits substituants non identiques étant des radicaux chloro, méthyle, méthoxy ou trifluorométhyle, à l'action de l'hydrogène en présence d'un catalyseur de métal noble jusqu'à ce que la réaction de réduction-hydrogènyse pour former l'acide 2-oxo-indoline-1-alcanoïque 3-substitué voulu de formule structurelle I ou II soit sensiblement totale et, le cas échéant, à transformer un composé répondant à ladite formule structurelle I ou II dans laquelle X¹ est un groupe méthoxy en un composé correspondant dans lequel X¹ est un groupe hydroxy puis, le cas échéant, à transformer ledit produit final acide en un ester d'alkyle en C₁-C₆ ou en un dérivé amide amide primaire d'un tel composé ou en un sel de base dudit acide avec un cation pharmacologiquement acceptable.

2. Procédé selon la revendication 1, caractérisé en ce que le groupe de blocage aralkyle de R dans la matière de départ de formule structurelle III ou IV est un radical benzyle.

3. Procédé selon la revendication 1, caractérisé en ce que le catalyseur de métal noble employé dans la réaction est du palladium sur carbone.

4. Procédé selon la revendication 1, caractérisé en ce que la réaction est mise en œuvre dans un solvant organique inerte vis-à-vis du milieu réactionnel en présence d'une quantité mineure d'acide.

5. Procédé selon la revendication 4, caractérisé en ce que la réaction est mise en œuvre à une pression comprise dans la gamme allant de 103,4 à 344,7 kPa à une température comprise dans la gamme allant d'environ 0°C à environ 50°C.

6. Procédé selon la revendication 1, dans lequel le composé préparé est l'acide 3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acétique.

7. Procédé selon la revendication 1, dans lequel le composé préparé est l'acide 3-(3,4-dichloro- α -méthylbenzyl)-2-oxo-indoline-1-acétique.

8. Procédé selon la revendication 1, dans lequel le composé préparé est l'acide 5-chloro-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acétique.

9. Procédé selon la revendication 1, dans lequel le composé préparé est l'acide 6-méthoxy-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acétique.

10. Procédé selon la revendication 1, dans lequel le composé préparé est l'acide 6-hydroxy-3-(3,4-dichlorobenzyl)-2-oxo-indoline-1-acétique.